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MAJOR CARDIOVASCULAR TRIALS WITH PRIMARY SURROGATE ENDPOINTS: 2006 TO 2011

Poster Contributions
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Background: Surrogate endpoint trials provide a means to test strategies more efficiently, but they are accompanied by some uncertainty about the relationship between changes in surrogate markers and clinical outcomes. We sought to determine recent trends in the publication of cardiovascular trials with surrogate outcomes.

Methods: We identified phase III and IV cardiovascular trials with primary surrogate endpoints published in NEJM, Lancet, and JAMA from Jan 2006-Dec 2011. The success of the trials in meeting the primary endpoint, and the unforeseen excess deaths were evaluated. We also tracked the above three journals for publication of clinical outcome trials on the interventions tested in surrogate trials. We determined which of the interventions were in routine medical use for tested indications as of the end of 2012.

Results: We screened 873 citations and identified 77 trials with a primary surrogate endpoint (46 drug trials, 8 device trials, 23 others). Overall, 54 trials (70.1%) were positive for the primary endpoint and 23 (29.9%) were negative; 5 trials showed significantly higher risk for cardiovascular events or death. For 12 of the 77 trials with primary surrogate endpoints, at least one subsequent clinical outcome study was published in one of these journals. Among these, 4 showed positive results in surrogate trials and outcome trials, 3 showed positive results for surrogates but negative results in outcome trials, and 5 were negative in both surrogate trials and clinical outcome trials. There was no study that showed negative results in a surrogate trial but subsequent positive clinical results. Thirty six of the tested interventions are being used in routine medical care and 41 are still considered experimental in the USA.

Conclusions: Cardiovascular surrogate outcomes trials are common, frequently show superiority of the tested intervention and infrequently are followed by a prominent outcomes trial. However, when there was a high profile outcomes study, about half of the positive surrogate trials were not validated. Cardiovascular surrogate trials may be better for excluding benefit from the patient perspective than for identifying it.